REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Shiga Toxin–Producing *Escherichia coli* and the Hemolytic–Uremic Syndrome

Stephen B. Freedman, M.D.C.M., Nicole C.A.J. van de Kar, M.D., and Phillip I. Tarr, M.D.

From the Departments of Pediatrics and Emergency Medicine, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada (S.B.F.); the Department of Pediatric Nephrology, Radboud Institute for Molecular Life Sciences, Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, the Netherlands (N.C.A.J.K.); and the Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, and the Department of Molecular Microbiology, Washington University School of Medicine, St. Louis (P.I.T.). Dr. Freedman can be contacted at stephen.freedman@ahs.ca or at Alberta Children's Hospital, C4-634, 28 Oki Dr. NW, Calgary, AB T3B 6A8, Canada.

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Shiga toxin–producing *Escherichia coli* (STEC) are bacteria that carry the genes producing Shiga toxins.[1] These pathogens have the potential to cause diarrhea, which is often bloody, and can trigger a thrombotic microangiopathy (TMA) that leads to the hemolytic–uremic syndrome (HUS), which is defined as thrombocytopenia (platelet count <150,000 per cubic millimeter), nonimmune hemolytic anemia (hematocrit <30%), and azotemia (creatinine level higher than the upper limit of the normal range).[2] Although a range of microbial pathogens can precipitate HUS, STEC are responsible for most cases in children worldwide.[3] Other notable infectious causes include *Streptococcus pneumoniae* and influenza virus.[4] TMA in both HUS and other conditions is often classified as primary or secondary. Atypical HUS (i.e., primary TMA) denotes an underlying regulatory defect in the complement system (i.e., primary disease), whereas secondary TMA is triggered by microbial factors that activate endothelial cells and the ensuing microangiopathic cascade (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[5,6] Rapid identification of the cause of TMA is important because it enables the institution of cause-specific therapy. Although the use of prompt anticomplement therapy in patients with atypical HUS improves kidney-related outcomes,[7] unwarranted use of such therapy can be detrimental.

History and Nomenclature

Forty years ago, *E. coli* O157:H7 was identified as a cause of bloody diarrhea.[8] Shortly thereafter, it was reported that the stools of children with HUS contain *E. coli* of varying serotypes (including O157:H7) that produce toxins that are lethal to cultured Vero cells.[9] These toxins, which are variably neutralized by antiserum to Shiga toxin produced by *Shigella dysenteriae* serotype 1, are thus referred to as Shiga toxins; synonyms include verotoxin, verocytotoxin, and Shiga-like toxin. Similarly, the bacteria that produce these toxins are referred to as STEC (Table S2). The two Shiga toxin families, Shiga toxin 1 and Shiga toxin 2, have different clinical implications. Shiga toxin 2–producing serotypes are much more virulent than Shiga toxin 1–producing serotypes, which rarely lead to HUS unless they also produce Shiga toxin 2.

Given their propensity to precipitate HUS on average 7 days after the onset of diarrhea, the subset of STEC that produce Shiga toxin 2 are referred to as "high risk."[10] Of the numerous high-risk serotypes, *E. coli* O157:H7 remains the best characterized, partly because its colonies are easily identifiable when plated on the appropriate culture medium, since they are usually colorless as a result of their inability to ferment sorbitol (Fig. S1).[11] We use the term *E. coli* O157 here to denote any STEC bearing this serogroup antigen; STEC-expressing O antigens other than O157 are termed non-O157 STEC.

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SHIGA TOXINS

Shiga toxin production is the cardinal virulence trait of STEC. Shiga toxin 1 and 2 each consist of a single A subunit and a pentameric B subunit, and they cause disease through pentameric B subunit binding to globotriaosylceramide (Gb3), a glycosphingolipid expressed by eukaryotic cells (Fig. 1). After binding, the holotoxin (still bound to Gb3) is internalized and trafficked in a retrograde manner through the Golgi apparatus and then to the endoplasmic reticulum. After proteolysis and reduction of a disulfide bond, the enzymatically active A_1 subunit targets 28s RNA of the large ribosomal subunit, where it cleaves a specific adenine residue and inhibits protein synthesis.[12]

The pathogenicity of STEC serotypes is determined primarily according to whether Shiga toxin 1, Shiga toxin 2, or both are expressed and, to a degree, according to the allelic variants of each Shiga toxin.[13] STEC that produce Shiga toxin 2 usually cause bloody diarrhea, as well as almost all cases of diarrhea-associated HUS[14] (Fig. 2). Since *E. coli* O157 almost universally produce Shiga toxin 2, they are always assumed to be high-risk STEC. Some STEC produce both Shiga toxins, and inexplicably, the risk of HUS is greater when the pathogen produces Shiga toxin 2 but not Shiga toxin 1.[13] The importance of toxin genotype and not *E. coli* serotype was exemplified by the 2011 Stx 2-producing *E. coli* O104:H4 outbreak, which caused more than 4000 infections in 16 countries, 908 HUS cases, and 50 deaths.[15]

EPIDEMIOLOGY

The incidence of STEC infection peaks during summer and fall and is greatest among children younger than 5 years of age, the group at highest risk for the development of HUS (Table 1). Predominant STEC serogroups vary according to region. *E. coli* O157 is the most commonly identified serogroup in the stool of symptomatic persons worldwide. It is currently identified in 84% of HUS cases in the United States.[18] However, *E. coli* O26, which causes less than 3% of cases of HUS in the United States, is the serogroup most often associated with HUS in the European Union.[16] Vehicles for *E. coli* O157 and non-O157 STEC outbreaks are similar, but meat exposure is more commonly associated with O157 outbreaks (Table S3 and Fig. S2). Expeditious reporting is encouraged because any infection could signify a previously undetected, ongoing outbreak. Daycare and household contacts should be monitored closely, since case clusters are common.

DIAGNOSIS OF STEC INFECTION

Early diagnosis of STEC infection is important for case management. Stool samples obtained from all patients with hematochezia and from children with nonbloody diarrhea accompanied by tenesmus or severe abdominal pain should be sent for bacterial pathogen detection.[21] The absence of fever does not preclude STEC infection.[22,23]

Laboratories use one or more strategies to identify STEC in stool, including pathogen isolation on agar, Shiga toxin detection on immunoassay, and identification of one or more Shiga toxin genes by means of nucleic acid amplification (Table 2). The ideal approach combines strategies to rapidly determine the presence of a high-risk pathogen. Because the ability to identify STEC in stool diminishes daily after the onset of diarrhea,[27] sensitivity is optimized by prompt acquisition and submission of specimens for testing. Thus, if a specimen of bulk stool is not immediately available, a rectal swab specimen should be obtained and processed. Although swabs are an acceptable alternative,[28,29] many laboratories insist on stool specimens; we urge clinicians to work with their microbiology colleagues to integrate rectal swab processing into their workflow. When the clinical suspicion of STEC infection is high, if rectal swabs are the initial specimen, stool should also be collected and tested when it becomes available.

E. coli O157 can be identified by serotyping a sorbitol-nonfermenting colony or detecting an O-antigen locus through DNA amplification. Although some other STEC serogroups (e.g., O80, O104, O113, O121, and O145) almost always produce Shiga toxin 2, toxin or toxin gene testing is easier to perform and more definitive than serogrouping for estimating the risk of HUS among patients with non-O157 STEC infections. Unfortunately, laboratory characterization of non-O157 STEC often fails to provide sufficient information (e.g., the presence or absence of Shiga toxin 2) to help the clinician gauge risk. In such circumstances, risk assessment should include the presence or absence of visibly bloody diarrhea (Fig. 2 and Table S4). Additional diagnostic strategies can be considered in special circumstances (Table S5).

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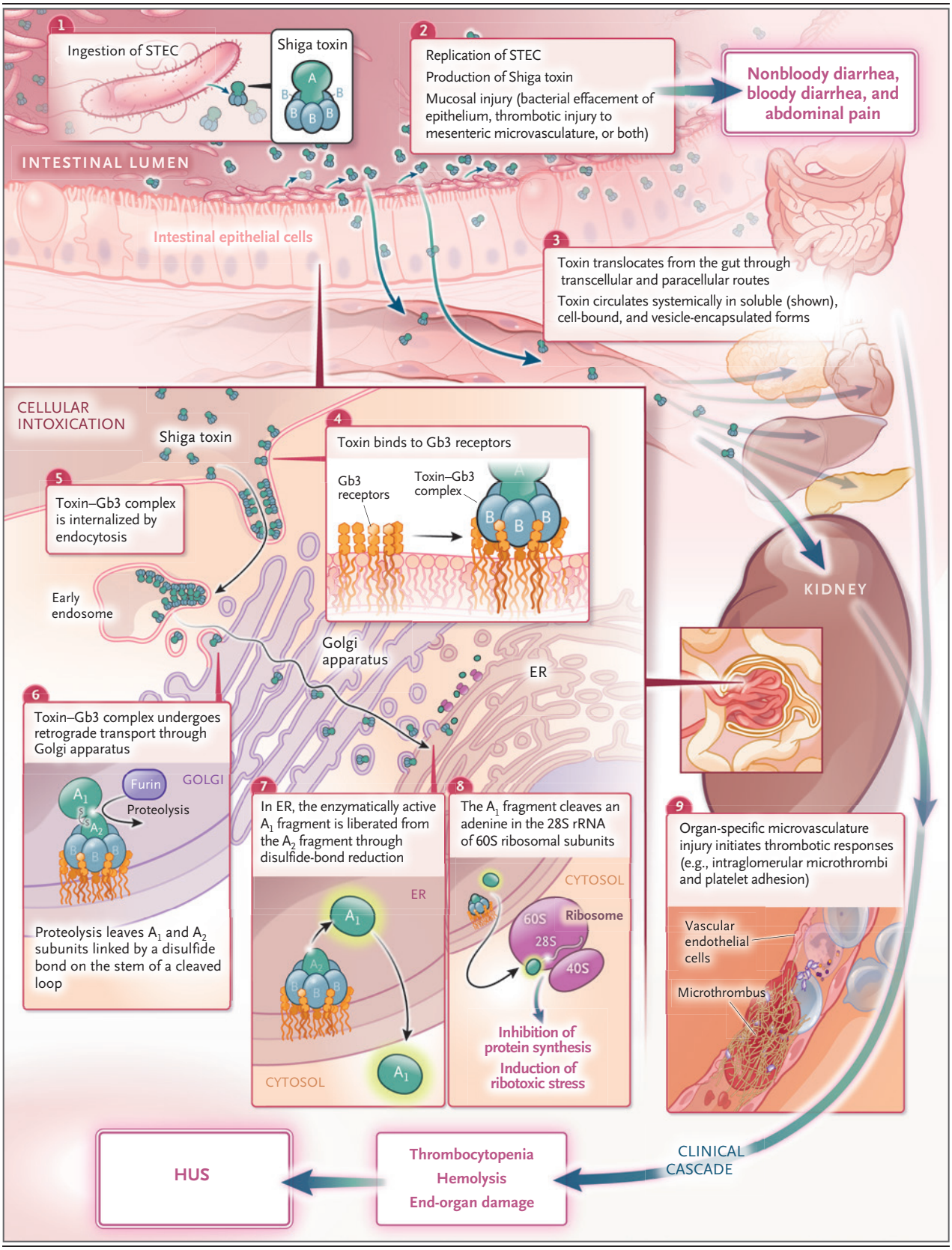

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Figure 1 (facing page). Pathophysiology of Shiga Toxin–Mediated Microangiopathy in Patients with Shiga Toxin–Producing *Escherichia coli* (STEC) Infection.

High-risk STEC are ingested from diverse sources (1). Infecting bacteria replicate in the intestines and express Shiga toxin 1, 2, or both; Shiga toxin 2 is more injurious to humans (2). The secreted toxins gain access to the circulation (3). Circulating toxin is thought to underlie the vascular injury leading to the hemolytic–uremic syndrome (HUS), with the most profound end-organ damage manifested in the kidneys. Postulated mediators include cytokines and chemokines (e.g., interleukin-6, interleukin-8, tumor necrosis factor α, and interleukin-1β), which can activate the extrinsic coagulation pathway. Shiga toxins (consisting of a single A and pentameric B subunits, referred to as AB_5) bind to cell-surface globotriaosylceramide (Gb3) through their B subunit (4). Shiga toxins (AB_5) bound to Gb3 (bound Gb3 not shown) enter the early endosome (5), which transports the complex to the Golgi apparatus (6). Intracellular Gb3 is necessary for toxic effects. Shiga toxins bound to Gb3 are then trafficked in a retrograde direction through the Golgi apparatus, where they are nicked by furin, leaving the A_1 and A_2 fragments of the A subunit attached by a disulfide bond. Nicked Shiga toxins are transferred to the endoplasmic reticulum (ER), where the disulfide bond joining the A_1 and A_2 fragments is cleaved (7). The liberated, enzymatically active A_1 subunit then removes an adenine from the 28S ribosomal RNA (rRNA) of the 60S ribosome, halting protein synthesis (8). Vascular injury caused by inhibition of protein synthesis, activation of inflammatory mediators, or both and initiated by circulation of Shiga toxins generates microvascular thrombi (9). Platelet trapping and red-cell fragmentation lead to thrombocytopenia and anemia, and the thrombi are postulated to underlie end-organ damage.

CLINICAL COURSE

LOW-RISK STEC

Few studies have characterized infections caused by STEC that produce Shiga toxin 1 but not Shiga toxin 2.[30,31] These low-risk pathogens usually cause nonbloody diarrhea[30] and they rarely lead to HUS,[14,32] except possibly among immunocompromised adults.[33]

HIGH-RISK STEC

The first day of diarrhea is usually considered the first day of illness, although in the prediarrheal phase, patients may have nonspecific symptoms such as abdominal pain, vomiting, and fever (Fig. S3). A median 3-day interval between exposure to high-risk STEC and the first loose stool has been reported.[34] An analysis of *E. coli* O157 cases reported to the U.K. National Enhanced STEC Surveillance System between 2014 and 2018 showed that in nearly two thirds of infections, visible blood appeared in the stool 1 to 3 days after diarrhea began.[30] The median number of stools in the 24 hours before presentation ranges from 7 to 11,[22,26] and the diarrhea usually abates by day 7 of illness. Defecation is often painful, and toilet-trained children may become incontinent. Fever is reported in 30 to 50% of infected children but often is absent when children present for care.[23,26,35]

We suggest daily laboratory testing to monitor all children infected with a known high-risk Shiga toxin (Shiga toxin 2 detected) or a suspected high-risk STEC (Shiga toxin detected but not genotyped in a patient with bloody diarrhea) until the window for the development of HUS has closed or repeat testing has revealed no evidence of a progressive microangiopathy. Thus, laboratory testing should continue until the platelet count increases by at least 5% in specimens obtained 24 hours apart on or after the fifth day of illness in the context of improving or resolved gastrointestinal symptoms.

Although the proportion of high-risk STEC-infected patients in whom HUS develops is influenced by many factors, large pediatric case series typically show that HUS develops in 15 to 20% of infected children, with the greatest risk among those who are younger than 5 years of age.[23,36] In a multinational study involving 927 STEC-infected children (<18 years of age) seen in an emergency department, 4% of the children presented with HUS, and HUS subsequently developed in an additional 14%.[23] These findings are in keeping with results from a meta-analysis of 17 studies involving 1896 infected persons, 18% of whom had HUS.[36] Although HUS almost always manifests between days 5 and 14 of illness,[35,37] microangiopathic changes are apparent by day 8 or 9, and anuria, if it occurs, rarely commences after day 10.[38] In illnesses that do not progress to the development of HUS, the platelet count often transiently decreases but remains within the normal range (Fig. S4A). A small proportion of children have thrombocytopenia and anemia but not azotemia (Fig. S4B). Rapidly progressive thrombocytopenia is the sentinel and universal hematologic abnormality in patients in whom HUS develops (Fig. S4C and S4D) and is often accompanied by hemoglobinuria and elevated serum lactate dehydrogenase

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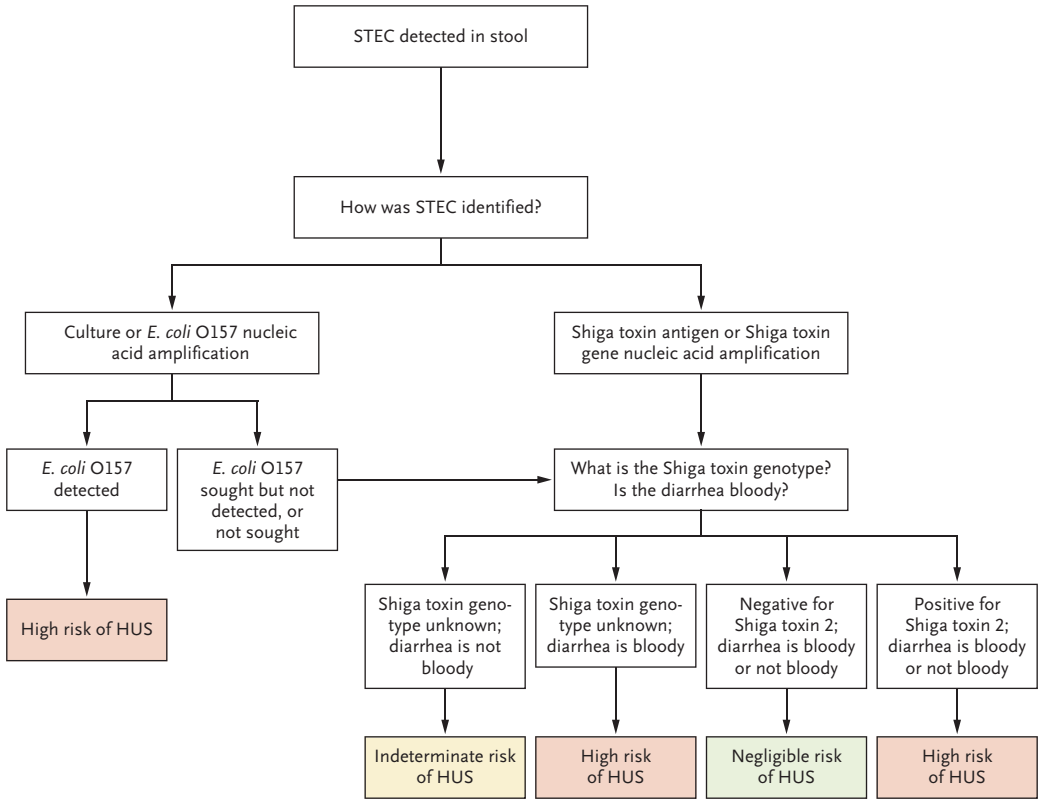
STEC detected in stool
How was STEC identified?
Culture or E. coli O157 nucleic acid amplification
Shiga toxin antigen or Shiga toxin gene nucleic acid amplification
E. coli O157 detected
E. coli O157 sought but not detected, or not sought
What is the Shiga toxin genotype? Is the diarrhea bloody?
High risk of HUS
Shiga toxin genotype unknown; diarrhea is not bloody
Shiga toxin genotype unknown; diarrhea is bloody
Negative for Shiga toxin 2; diarrhea is bloody or not bloody
Positive for Shiga toxin 2; diarrhea is bloody or not bloody
Indeterminate risk of HUS
High risk of HUS
Negligible risk of HUS
High risk of HUS

Figure 2. Assessing the Risk of HUS among Patients with STEC Infection.

High-risk infections are due to STEC that produce Shiga toxin 2 and can therefore cause HUS. Children younger than 5 years of age have the greatest likelihood of this outcome (15 to 20%). Low-risk infections produce Shiga toxin 1 but not Shiga toxin 2 and are extremely unlikely to cause HUS. In patients with indeterminate Shiga toxin findings, the risk is challenging to quantify, so treatment of such patients should be guided by various other factors (e.g., age, local epidemiologic factors, the presence or absence of bloody diarrhea, clinical status, and duration of diarrhea) until Shiga toxin genotyping is known or the at-risk period has elapsed. *E. coli* O157 are detected by culture or nucleic acid amplification and are considered to convey high risk because they almost always produce Shiga toxin 2. If the genotype is not known, the patient should be monitored for a high-risk infection until Shiga toxin 2 has been ruled out. In North America and Argentina, *E. coli* O157 remain the predominant cause of HUS. Hence, if *E. coli* O157 has been ruled out, the likelihood of a high-risk STEC infection is reduced but not eliminated. STEC serogroups O26 (mainly in European isolates), O80, O104, O111, O113, O121, and O145 frequently produce Shiga toxin 2, but most isolates of other non-O157 STEC serogroups do not. In practice, aside from O157, serogroups are rarely determined in a clinically useful interval. Thus, risk is most precisely determined on the basis of the Shiga toxin genotype, not the serogroup. The absence of bloody diarrhea reduces but does not eliminate the likelihood that a high-risk STEC infection is present. Similarly, the exclusion of *E. coli* O157 reduces but does not eliminate the likelihood that a high-risk STEC infection is present. Toxin genotyping is needed to more precisely define the risk.

levels.[39] Hemoglobinuria reflects intravascular hemolysis, the depletion of circulating haptoglobin, and plasma hemoglobin levels that exceed the reabsorptive capacity of the kidneys. If the increase in serum creatinine levels is disproportionate to the decrease in the hematocrit, the ensuing HUS is often severe (Table S6).[40,41]

POSTULATED PATHOPHYSIOLOGY OF STEC-RELATED DIARRHEA AND HUS

Activation of the microvascular endothelium is hypothesized to be a major contributor to the gastrointestinal manifestations of STEC infection. Colonic histologic assessment early in the

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Table 1. Epidemiologic Features of Shiga Toxin–Producing *Escherichia coli* (STEC) Infection.*

Location and Year	Most Common STEC Serogroups		Age Distribution		STEC Serogroups in HUS	
	Serogroup	Distribution	Age	Distribution	Serogroup	Distribution
		percent		*percent or incidence/total population*		*percent*
Europe†						
2021	O157	15.2	—	—	O26	34.0
	O26	14.8	—	—	O157	19.6
	Not reported	44.1	—	—	O80	11.0
	Nontypable	25.9	—	—	O145	7.6
	—	—	—	—	Not reported	27.8
2020	—	—	0–4 yr	27.8	—	—
	—	—	5–14 yr	12.8	—	—
	—	—	15–24 yr	8.9	—	—
	—	—	25–44 yr	14.1	—	—
	—	—	45–64 yr	15.4	—	—
	—	—	≥65 yr	21.2	—	—
United States‡§						
2016–2020	O157	15.8	0–4 yr	18.7/100,000	O157	83.9
	O26	7.9	5–9 yr	5.4/100,000	O111	5.7
	O103	7.9	10–19 yr	5.7/100,000	O145	3.8
	O111	5.1	20–64 yr	3.8/100,000	O26	2.8
	Other	12.9	≥65 yr	4.8/100,000	Undetermined	2.4
	Culture-independent diagnostic test	44.1	—	—	Other	1.4
	Non-O157, not serogrouped	6.3	—	—	—	—
Argentina¶						
2018–2019	O157	31.0	Mean, 36.1±30.1 mo		—	—
	O145	20.7	Median, 24.0 mo (IQR, 15–47)		—	—
	O26	13.8	—	—	—	—
	O121	3.4	—	—	—	—
	Other	17.3	—	—	—	—
	Nontypable	13.8	—	—	—	—
2005–2016‖	—	—	—	—	O157	73.6
	—	—	—	—	O145	16.8
	—	—	—	—	O121	5.4
	—	—	—	—	O26	0.7
	—	—	—	—	O103	0.7

* Percentages may not sum to 100 because of rounding. HUS denotes hemolytic–uremic syndrome, and IQR interquartile range.
† Data are from the European Food Safety Authority, European Center for Disease Prevention and Control.[16,17] In the category of most common STEC serogroups, the year 2020 was the first year that the United Kingdom was not included in the European Union One Health report, a change that could explain the proportional increase in O26 STEC infections and decrease in O157 STEC infections in the European Union.
‡ Data are from the Centers for Disease Control and Prevention[18] FoodNet surveillance system, which covers 15% of the U.S. population.
§ Data on STEC serogroups in HUS are for culture-confirmed STEC infection, which accounted for 67% of all cases of diarrheal-associated HUS in children.
¶ Data are from Rivas et al.[19] (for the most common STEC serogroups and age distribution) and Alconcher et al.[20] (for STEC serogroups in HUS). Data for the most common STEC serogroups are limited to a network of 25 hospitals, with 29 STEC cases, in 6 provinces and to children with bloody diarrhea who were younger than 10 years of age.
‖ Data for the most common STEC serogroups are national surveillance data, limited to children younger than 18 years of age.

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Table 2. Approaches to Detecting STEC in Human Stool.

Method	Comments	Limitations	Clinical Implications	Disease Control Implications
Agar-based isolation				
Sorbitol–MacConkey agar, with or without tellurite and cefixime	Detects colorless, sorbitol-nonfermenting *E. coli* O157; tellurite and cefixime in the agar increase sensitivity	Does not detect sorbitol-fermenting non-O157 STEC or a clone of the high-risk O157:HNM that ferments sorbitol[24]	If *E. coli* O157 is confirmed by antigen detection, high-risk infection can be assumed	*E. coli* O157 isolation on agar is necessary for DNA fingerprinting and case investigations
Multiindicator chromogenic agar[25]	Detects sorbitol-nonfermenting *E. coli* O157 and many non-O157 STEC	Fails to detect all toxin-producing strains and does not identify toxin genotype	If *E. coli* O157 is confirmed by antigen detection, high-risk STEC should be assumed; detection of non-O157 by this method requires toxin genotyping to assess risk	Isolation of STEC on agar is necessary for DNA fingerprinting and case investigations
Shiga toxin antigen detection in broth culture of stool	Theoretically detects STEC independently of serotype	Toxin immunoassays are less sensitive than chromogenic agar plating for the detection of *E. coli* O157[26]; some Shiga toxin antigen assays do not identify toxin genotype; antigen detection should not be used as the sole screening method	If the assay identifies Shiga toxin 2, the patient has a high-risk STEC infection; if the assay identifies the presence of Shiga toxin 1 and the absence of Shiga toxin 2, the patient does not have a high-risk STEC infection	The pathogen should be isolated from the broth or, ideally, from a parallel inoculated agar plate for DNA fingerprinting and case investigations
Detection of genes encoding Shiga toxins	Detects STEC independently of serogroup, does not depend on toxin production, and is probably the most sensitive technique	Commercially available devices rarely convey toxin genotype; this technique does not yield an isolate	If the readout explicitly states that Shiga toxin 2 is present or that a locus encoding the O157 antigen is found, the patient has a high-risk STEC infection	This technique does not isolate STEC on agar, which is necessary for DNA fingerprinting and case investigations

illness shows superficial inflammation and focal necrosis with preserved deep crypts,[42] findings that suggest ischemia. Ischemia may be the consequence of prothrombotic and proinflammatory injury during the initial diarrheal phase,[43] triggered by Shiga toxin circulation, with subsequent damage to the microvascular endothelium.[44-46] Hematologic abnormalities noted in the diarrheal phase include increased circulating plasminogen activator inhibitor type 1 activity; elevated concentrations of D dimer, prothrombin activation fragments 1 and 2,[47] and platelet-activating factor[48]; sheared von Willebrand factor[49]; and dysregulated angiopoietin 1 and 2 activity.[43] Thrombotic microvascular injury has been considered a major factor in the progression to HUS, given the identification at autopsy of microvascular thromboses in the kidneys, brain, heart, and other extraintestinal organs.[50]

CLINICAL COURSE AND COMPLICATIONS OF STEC-RELATED HUS

Oligoanuria has been reported in 50 to 60% of children in whom STEC-associated HUS developed.[22] Most children with oligoanuria receive kidney-replacement therapy until urine flow resumes, which usually occurs within 2 weeks after the initiation of dialysis.[51] The case–fatality rate for STEC-associated HUS remains approximately 3% among children[40] and up to 20% among middle-aged and older adults.[33] Such deaths are rarely attributable to a single cause, but complications such as seizures, coma, and stroke appear to be particularly ominous.[51,52] Cardiac involvement, including ischemia, arrhythmias, cardiomyopathy, and pericardial effusion, has been reported in less than 10% of children with

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HUS.[53] Rarely, catastrophic intestinal events such as bowel necrosis and perforation occur.[54]

Other acute complications of varying severity and frequency include hypertension, symptomatic pancreatitis or asymptomatic elevation in lipase levels, elevations in aminotransferase levels, cholestasis, respiratory distress syndrome, pulmonary hemorrhage, central volume overload, pleural effusion, insulin-dependent hyperglycemia, and disseminated intravascular coagulation. Gallstones and intestinal strictures have been reported in some patients in the year after HUS resolution.[55]

Chronic kidney disease can become apparent at variable intervals after the acute HUS episode. It is associated with the duration of anuria, receipt of kidney-replacement therapy, or both during HUS, and it has a variable prognosis.[55-59] A recent report suggests that chronic kidney injury can be detected in up to one third of children who have had HUS but did not receive kidney-replacement therapy.[60] Although end-stage kidney disease is uncommon, hypertension, proteinuria, and a reduced glomerular filtration rate can manifest years after the acute episode of STEC-related HUS. Therefore, it is prudent to monitor patients[55] throughout their childhood for renal sequelae. Data on outcomes in adults are lacking.

COMPLEMENT ACTIVATION IN STEC-RELATED HUS

Complement activation, induced by the intestinal infection or, as shown in vitro, by Shiga toxin itself,[61] may play a role in STEC-related HUS.[62,63] During the acute illness, a decrease in C3 and C4 has been reported, along with a concomitant increase in complement breakdown products.[64] However, on the basis of current data, screening for complement regulatory gene mutations is not warranted in most cases of STEC-associated HUS. Even if a pathogenic genetic variant is identified, such variants are not associated with the severity of illness, as reported in a study involving 75 children with STEC-related HUS.[65]

MANAGEMENT

If STEC infection is strongly suspected, the hemoglobin level, hematocrit, platelet count, and urea, creatinine, and electrolyte levels, along with a blood smear, should be assessed on initial evaluation and monitored during the illness. Baseline values are useful because they aid in the interpretation of repeat tests obtained 1 or 2 days later. Such repeat tests, which may be within the normal range, can aid clinicians in more accurately identifying early microangiopathy as reflected by decreasing platelet counts and hemoglobin levels or increasing creatinine levels. Elevated lactate dehydrogenase levels[23] may also be an early marker of progression to HUS, and their clinical usefulness warrants further study.

It is important to avoid potentially harmful interventions in patients with possible or confirmed STEC infection. Multiple studies have shown an association between antibiotic administration and an increased risk of HUS among patients infected with high-risk STEC.[36] Thus, avoiding empirical antibiotic administration in immunocompetent patients with bloody diarrhea is important.[21] Although it is tempting to try to relieve abdominal pain, narcotics and antimotility drugs have been observed to prolong bloody diarrhea in *E. coli* O157 infection[66] and to increase the risk of HUS and neurologic complications.[66,67] Nonsteroidal antiinflammatory drugs can cause acute kidney injury during gastrointestinal infection and are best avoided.[68] Although a single dose of oral ondansetron facilitates oral rehydration in children with acute gastroenteritis, multiple doses and intravenous administration have no added benefit,[69] can increase the frequency of diarrhea, and may prolong the QT interval.[70] Thus, multiple doses and intravenous administration should not be routinely used.

VOLUME EXPANSION

Patients with higher relative hematocrit or hemoglobin values (probably reflecting hemoconcentration) when HUS is first diagnosed have been shown to have worse outcomes (Fig. S4E). Such patients are more likely to receive kidney-replacement therapy and have increased risks of neurologic complications and death.[71] Hence, when a child is suspected of being infected with a high-risk STEC pathogen, the administration of intravenous isotonic fluids while the results of blood tests are pending is a simple and potentially beneficial intervention. Furthermore, observational studies have associated administration of

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intravenous fluid before HUS has been confirmed with a reduced incidence of anuria and a shorter hospital stay.[37,38] In addition, two nonrandomized studies that compared isotonic volume expansion early in the course of HUS with the historical practice of restricting fluids provide further support for intravascular volume expansion. In one study, infusion of 0.9% sodium chloride to achieve a target weight of 7 to 10% over the presumed preillness weight was associated with reduced use of kidney-replacement therapy, fewer long-term sequelae, and fewer days spent in the hospital and intensive care unit (ICU).[72] In the other study, children receiving 10 ml of isotonic crystalloid per kilogram per hour over a period of 3 hours, followed by the administration of maintenance isotonic fluids for the next 48 hours, were less likely to receive kidney-replacement therapy during the course of their illness.[73] Although these studies showed no complications attributable to intravenous volume expansion, fluid overload has long been associated with increased morbidity and mortality among critically ill children with acute kidney injury from other causes and remains a potential concern.[74]

In view of the nonrandomized nature of these studies, as well as a recent series showing contradictory findings among young adults hospitalized with STEC infection,[75] the costs of hospitalizing all STEC-infected children, and risks associated with fluid overload, evidence from clinical trials of a benefit of volume expansion is required to support its routine use. A reasonable alternative approach is to perform daily biochemical, hematologic, and clinical monitoring for evolving microangiopathy and dehydration and the treatment of the latter through the provision of oral or intravenous fluids, on an inpatient or outpatient basis, according to the patient's pain and hydration needs, until the at-risk period has ended.

KIDNEY-REPLACEMENT THERAPY

In many case series, more than 50% of patients with STEC-related HUS received kidney-replacement therapy.[23] Indications in patients with HUS, as in patients with other forms of acute kidney injury, depend on the extent of the kidney injury and the related abnormalities. Severe electrolyte or acid–base imbalances, uremic symptoms, fluid overload that does not respond to conservative measures, and the need to advance nutrition all warrant kidney-replacement therapy. Although peritoneal dialysis is relatively safe, is effective,[76] and involves technology that avoids the need for anticoagulant therapy and placement of a central venous catheter, potential complications include peritoneal catheter malfunction, peritonitis, and fluid leakage. Prophylactic antibiotics are usually administered perioperatively to reduce the risk of peritonitis in children undergoing catheter insertion for peritoneal dialysis.[76] Hemodialysis should be considered when rapid fluid and solute removal is required and has been more commonly used in older children and adults. However, thrombocytopenia-associated bleeding during catheter insertion, catheter malfunction, and catheter-related sepsis are potential complications.[77] Since hemodialysis and peritoneal dialysis are likely to be equivalent with respect to the survival benefit for patients with acute kidney injury,[77] the choice between the two types of dialysis has usually reflected patient characteristics, local expertise, and resources.[78]

Continuous kidney-replacement therapy should be considered for children with hemodynamic instability and multiorgan dysfunction, since it has fewer hemodynamic and intracranial pressure effects yet provides efficient solute removal.[79] However, continuous kidney-replacement therapy has disadvantages. It requires anticoagulant therapy and is usually performed only in children admitted to the ICU.[77]

BLOOD PRODUCTS AND CATHETER PLACEMENT

Packed red-cell transfusions are administered to most patients with STEC-associated HUS.[40] Because most HUS complications are related to thrombotic injury, platelet infusions should be limited to patients with hemodynamically significant bleeding. Depending on surgical experience and approach, peritoneal dialysis catheters can usually be inserted without platelet transfusion, although platelets are generally given before insertion of a central venous catheter.[76]

TOXIN NEUTRALIZATION

Because systemic toxemia is likely to precede HUS, strategies for neutralizing extraintestinal toxin early in the course of STEC infection are appealing. However, only a minority of infected children have quantifiable levels of circulating Shiga toxin 2 in the first days of diarrhea, and even among these children, toxemia is short-lived.[27,45] Thus, the opportunity to neutralize extraintestinal Shiga toxin before the postulated "hit and run" vascular injury occurs might be limited.

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Nonetheless, since Shiga toxin 2 has been identified in serum and in or on circulating blood cells and microvesicles shortly before or during HUS, extraintestinal Shiga toxin remains a potential therapeutic target.[46,80]

COMPLEMENT INHIBITION

Several disease-modifying treatments have been proposed for STEC-associated HUS. Eculizumab, an anti-C5 monoclonal antibody, is highly effective in atypical HUS, but only rarely do patients with STEC-associated HUS have complement gene variants that are pathogenic.[65] Although profiles of circulating complement protein in STEC-associated HUS are often abnormal,[64,81] studies have not shown the value of eculizumab in STEC-associated HUS,[33,82,83,84] and kidney-biopsy specimens obtained from patients with STEC-associated HUS show no evidence of complement-mediated injury.[85] Furthermore, complement activation has not been observed in a primate model of Shiga toxin–induced microangiopathy.[86] The complement component C5, as part of the terminal complement pathway, is an important component of the host defense against encapsulated bacteria, and the use of eculizumab to inhibit C5 has been associated with severe infection by a variety of bacteria, including *Neisseria meningitidis* and other neisseria species, as well as *Pseudomonas aeruginosa* and *Moraxella lacunata*.[87] Hence, the use of eculizumab in STEC-associated HUS should be limited to clinical trials.

PLASMA EXCHANGE

Although plasma exchange is beneficial in patients with thrombotic thrombocytopenia purpura because it corrects the absence or dysfunction of ADAMTS13, evidence to support its use in those with STEC-associated HUS is extremely limited. Two small studies with substantial methodologic limitations showed benefits associated with the early use of plasma exchange in older adults.[88,89] However, no benefits were identified in a study of the STEC-associated HUS outbreak in Germany in 2011[83] or in pediatric studies.[90,91] Thus, given the associated risks, plasma exchange is not currently recommended.[92]

RISK FACTORS FOR ADVERSE OUTCOMES

After establishing the presence of a high-risk STEC infection in a patient with diarrhea, an assessment of risk factors can offer some guidance about the likelihood that HUS will develop (Table 3). Modifiable risk factors include the use of antibiotics,[36] narcotics, and antidiarrheal medications; dehydration; relative hemoconcentration[71]; and hyponatremia.[23] Unmodifiable risk factors include age (increased risk at <5 years[23] and >75 years[94]); female sex; the presence of bloody diarrhea, vomiting, or both; the presence or absence of Shiga toxin 1 (absence correlates with higher risk)[14]; elevated white-cell count (≥13,000 per cubic millimeter)[23,66]; and a platelet

Table 3. Factors Associated with Progression from High-Risk STEC Infection to HUS and for the Development of Severe HUS.

Risk factors for progression from STEC infection to HUS
Unmodifiable risk factors
Younger age (<5 yr)[23,66,93]
Older age (>75 yr)[94]
Female sex[93]
Bloody diarrhea, vomiting, or both[35,66,94]
Absence of Shiga toxin 1[13,14,32,93]
White-cell count ≥13,000/mm^3[35,45,66,94]
Initial platelet count <250,000/mm^3[23]
Modifiable or possibly modifiable risk factors
Use of antibiotics[35,36,93]
Use of narcotic and antidiarrheal medication[66,95]
Hemoconcentration, dehydration, or both[23]
Hyponatremia[23]
Risk factors for progression to severe HUS
During pre-HUS phase
Unmodifiable risk factors
Shorter diarrheal prodrome[51]
Modifiable or possibly modifiable risk factors
Hyponatremia[23]
Lack of parenteral volume expansion[37,38]
Delayed pathogen identification[37]
Administration of antibiotics[35]
At time of HUS diagnosis
Unmodifiable risk factors
Hypocalcemia[96]
Central nervous system involvement[41]
Increased neutrophil count[51]
Modifiable or possibly modifiable risk factors
Relative hemoconcentration[51,71]
Hyponatremia[41]

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count below 250,000 per cubic millimeter.[23] When a diagnosis of HUS is established, similar assessment can be used to gauge the possibility of a complicated course. At this point, dehydration, relative hemoconcentration,[23] hyponatremia,[41] and hypoalbuminemia are potentially modifiable risks for severe HUS or death.[97] An antecedent respiratory infection is an unmodifiable risk factor that is associated with poor outcomes.[40]

Formal risk score systems[98] are insufficiently sensitive to guide clinical care during the early stages of STEC infection or HUS.[99] Since rapid toxin genotyping provides substantial prognostic guidance, working with clinical laboratories to provide such information appears to be important. Knowledge of the timeline and platelet count in each patient can be helpful, since thrombocytopenia has long been observed as the first laboratory abnormality during the development of HUS.[83] In a patient who appears relatively well and whose clinical condition is improving, a stable or increasing platelet count on or after day 5 of illness is thought to be a reliable indicator that vascular injury has peaked and will soon improve.

CONCLUSIONS

STEC infection causes severe illness, particularly in children. Diagnostic approaches that include the testing of all children with bloody diarrhea for bacterial pathogens with the use of techniques that can identify O157 and non-O157 STEC, the use of rectal swabs to obtain specimens when stool specimens are unavailable, and reporting toxin genotypes when STEC are identified, are important components of care. Close monitoring of persons infected with high-risk STEC, avoidance of potentially harmful interventions, and prevention of volume depletion may avert complications. Unless and until specific treatments emerge, the possibility of adverse outcomes in a patient with a high-risk STEC infection must be considered. Thus, it is important to monitor the evolution of the disease and mitigae, to the extent possible, modifiable risk factors to improve outcomes.

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